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examination, including screening and treatment for strabismus, myopia, and lens dislocation, is recommended. Patients should be referred for genetic counseling, including psychosocial support and recurrence risk assessment for patients and relatives. The Marfan Syndrome Foundation (http://www.marfan.org) is a resource for patients, family members, and health care professionals. Information about clinical experts is available through this organization.

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Genetics for targeting disease prevention: diabetes

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The completion of the Human Genome Project and the discoveries of genes and gene variants associated with numerous common diseases have led to great expectations about not only deciphering the underlying causes of these diseases, but also preventing or curing them. Although the full realization of the promise of genomics is likely years off, insights gained over the last few years can strengthen clinical disease prevention efforts today.

Diabetes mellitus serves as a valuable model for exploring how emerging "genomic" concepts, tools, and knowledge might be applied in clinical practice to target disease prevention. With a few rare exceptions, most cases of diabetes are the manifestation of a complex interplay between underlying genetic factors and environmental influences. The increasing prevalence of diabetes, the enormous social and economic costs associated with the condition and its complications, and convincing evidence that prevention is possible all contribute to the intense research efforts currently focused on this disease. As more is learned about the underlying pathogenesis of diabetes, including the role of various genetic components, primary care clinicians will be called on increasingly to incorporate this knowledge into routine clinical care and to translate this knowledge into meaningful information for patients.

This article provides an overview of current thinking regarding genetics and diabetes (type 1, type 2, and gestational diabetes mellitus [GDM]), including a selective look at a few implicated gene variants. This article explores how this information might be applied in current and future clinical practice to do the following:

- Predict who is at risk for diabetes and its complications
- Identify and intervene to prevent or delay the development of diabetes in persons at risk

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- Identify patients with diabetes in an early stage and intervene to prevent later complications
- Individualize therapy for patients with diabetes to improve outcomes

The article concludes with some general thoughts about genetics and diabetes prevention in the future.

Diabetes overview

Diabetes mellitus is one of the most prevalent, serious, and costly health care problems today. Currently, 17 million people in the United States have diabetes, 5.9 million of whom are undiagnosed [1]. This number is expected to rise to 29 million diagnosed cases of diabetes by 2050, with the fastest growing rate in African Americans [2]. More than 151 million people are affected worldwide [3]. In 2000, diabetes was the sixth leading cause of death and the leading cause of blindness, kidney failure, and amputation in the United States [1]. The disease has a significant impact on primary care practice, being one of the top four diagnoses associated with ambulatory care visits in the United States in 2002 [4]. The condition, its treatment, and particularly its complications cost the United States $132 billion each year, with $91.8 billion in direct medical costs and $40.2 billion in indirect costs, including disability, work loss, and premature mortality [5].

Diabetes is actually a group of heterogeneous disorders characterized by abnormalities in insulin production or function. The hallmark feature of diabetes is elevated blood glucose, which over time is associated with numerous microvascular complications, including nephropathy, retinopathy, and neuropathy. Macrovascular complications occur, including coronary artery disease and peripheral arterial disease. The disease typically is divided into two main types—type 1 (previously called *juvenile* or *insulin-dependent diabetes mellitus*) and type 2 (previously called *adult-onset* or *non–insulin-dependent diabetes mellitus*). Many less common varieties also exist, including diabetes caused by rare monogenic (single-gene) disorders. It is being increasingly recognized that even within the two main types, there is considerable heterogeneity in terms of disease etiology and presentation. It is expected that studies of the genetic pathways leading to diabetes will continue to shed light on this heterogeneity and may serve as a foundation for future refinement of the classification system for the disease [5].

Approximately 5% of diabetes cases fall into the type 1 category [1]. Type 1 diabetes is characterized by an absolute deficiency of insulin resulting primarily from autoimmune destruction of the pancreatic islet cells (also called *beta cells*). This type of diabetes eventually requires exogenous insulin treatment for survival. The disorder typically presents in childhood or adolescence, affecting 1 out of every 400 to 500 children [1]. Type 1 diabetes aggregates in families, although only 10% of individuals who develop the

disease have a known family history [6]. Whites are at higher risk than members of other ethnic groups. The risk of type 1 diabetes in an individual with a family history is approximately four times greater than the risk in individuals without a family history. Risk to a child of a parent with type 1 diabetes is 11 times higher than controls, whereas risk to siblings is 20 times higher than controls [7]. Research has shown that it is possible to identify individuals at increased genetic risk for the disease and to predict who will go on to develop the disease by monitoring the development of autoimmune markers [8]. Primary prevention of type 1 diabetes is not yet possible, although it is an area of intense investigation [9].

Type 2 diabetes is the most common form of disease, accounting for 90% to 95% of cases [1]. Type 2 diabetes is characterized by abnormalities in insulin secretion or insulin action (ie, insulin resistance). The disease typically is found in middle-aged to older adults, although it is increasingly prevalent in children and adolescents [10]. The disorder is closely, but not exclusively, linked to obesity. Similar to type 1 diabetes, the disorder also tends to run in families. Having a mother with type 2 diabetes approximately doubles one's relative risk (RR 1.72–2.51). Having a father with type 2 diabetes increases risk less strongly (RR 1.22–1.69). Having both parents with the disease nearly quadruples risk (RR 2.42–5.61) [11,12]. Younger age of diabetes onset seems to increase the risk for diabetes in relatives [13]. In contrast to type 1, the risk of type 2 diabetes is greatest in nonwhite ethnic groups, including African Americans, Native Americans, Hispanics, and Southeast Asians [1]. Hispanics have the greatest estimated lifetime risk of developing the disease—45% for Hispanic males and 52% for Hispanic females born in 2000 [14]. The disorder typically can be treated with diet, exercise, and oral hypoglycemic agents, although some individuals eventually need insulin for glycemic control. The development of diabetes is a progressive process and includes a "prediabetes" stage, when abnormalities in glucose metabolism are evident and blood glucose levels begin to rise above the normal range. Of overweight adults between the ages of 45 and 74 years, an estimated 23% currently have prediabetes, characterized by impaired glucose tolerance, impaired fasting glucose, or both [15]. Trials have shown that the development of diabetes can be prevented or delayed in many individuals with prediabetes through lifestyle and medication interventions [16,17].

GDM is characterized by glucose intolerance during pregnancy. Approximately 7% of pregnant women in the United States have GDM annually [1]. Infants of mothers with GDM tend to be large (macrosomic) and are at higher risk of congenital anomalies [18]. Diabetes mellitus typically subsides after pregnancy, but GDM is closely associated with the later development of type 2 diabetes in 20% to 50% of affected women [1]. Family history of type 2 diabetes is a significant risk factor for developing GDM [19]. Individuals exposed to a diabetic milieu in utero also are at higher risk of developing type 2 diabetes later in life [20].

Genetic basis of diabetes

Overview

The familial nature of diabetes has been recognized for many years. Important discoveries regarding genetic factors associated with type 1 diabetes were made in the 1970s, but only in the last several years has significant progress been made to uncover specific gene variants associated with type 2 diabetes. Despite important advances, this work has been fraught with difficulty, and much challenging work remains [21].

Although there are rare forms of diabetes that are caused by single-gene mutations (eg, the disorders referred to as *maturity onset diabetes of the young* [MODY]), most cases of diabetes are believed to be polygenic, impacted by numerous genes. Disease risk results from the interaction of multiple genes and gene variants, their products or functions (or lack of products or functions), and the environment. Independently, each gene or variant likely contributes only a modest degree of risk or protection through a relatively minor change in gene product or function. The sum total of an individual's genes and lifetime environmental exposures determines whether the disease phenotype becomes manifest. Many of the variants that convey risk are believed to be fairly common in the population, which helps explain the prevalence of disease and explains why the gene variants have been difficult to pinpoint. Large numbers of people have the risk genotype but do not have the disease because they lack the other genetic or environmental triggers needed to develop the disease.

Genetics of type 1 diabetes

Approximately 60% of the gene variants conferring risk for type 1 diabetes are known [21]. Work continues to identify the remaining 40%. Most of the work on type 1 susceptibility genes to date has focused on the major histocompatibility complex human leukocyte antigens (HLA) and their associated genes on chromosome 6 [22]. Approximately 45% of familial aggregation of type 1 diabetes is associated with the HLA genes, in particular the HLA class II genes DQ and DR. DRB1*03 and DRB1*04 are "risk alleles," particularly when an individual is heterozygous DRB1*03/04 and positive for DQB1*0302. The DRB1*15/*16 (DR2) genotype seems to provide dominant protection against developing type 1 diabetes. Although certain known HLA variants and combinations confer risk, even those with the highest risk genotypes only go on to develop disease 8% of the time [8]. Other environmental or genetic factors must be present to trigger the development of disease.

Variation at a particular locus on the insulin gene (*INS*), referred to as the *variable repeat locus* (VNTR), also has been linked to type 1 diabetes [23]. Class I genes (genetic variants with fewer repeated segments at the VNTR locus) are associated with higher risk of type 1 diabetes, whereas

class II and III genes, which contain a larger number of repeated segments, are not. The various classes of genes at this locus are associated with ancestry; class II genes are uncommon in individuals with white ancestry.

Genetics of type 2 diabetes

Specific genes and gene variants associated with type 2 diabetes and its associated metabolic abnormalities are less well defined than those of type 1 diabetes. More than 40 different gene-disease associations have been suggested, although many have not held up in replication studies [21].

Genes associated with MODY have served as a starting point for investigating the genetics of type 2 diabetes [24]. MODY is characterized by a non–insulin-dependent diabetes that develops before age 25 years. It is inherited in an autosomal dominant fashion and is not associated with obesity. Single-gene mutations in six different genes, including various hepatocyte nuclear factor genes (4α, 1α, and 1β), account for 80% of all cases of MODY [25,26]. Although helpful in elucidating various metabolic pathways that when altered may lead to diabetes, research into the associations of the MODY genes with type 2 diabetes has not yielded much that is applicable to prevention.

In contrast to the autosomal dominant inheritance of MODY, the inheritance of type 2 diabetes is complex. Many studies have suggested increased transmission through maternal lines [27–29]. The maternal association has raised speculation about a possible role for mitochondrial genes in disease susceptibility because these genes are passed on exclusively through the mother [30]. Possible mitochrondrial gene variants have been identified, but more study is needed in this area [31]. It is likely that mitochondrial and nuclear genetic factors have a role in the development of type 2 diabetes, and it is possible that a paternally inherited factor may increase the risk associated with maternally inherited mitochondrial factors [31].

Genetic variations in genes coding for a variety of different molecules involved in glucose metabolism have been implicated in the development of type 2 diabetes. Only a few gene-disease associations have been replicated in more than one study at a level of significance suggesting a possible role in disease etiology. Specific single nucleotide changes or polymorphisms in genes for the sulfonylurea receptor, glucagon receptor, glucokinase enzyme, specific potassium channels, glucose transporter, and peroxisome proliferator-activated receptor (PPAR) molecules all have been linked to type 2 diabetes in more than one study [21].

The *PPAR γ2* gene has received considerable attention, not only for its role in type 2 diabetes, but also for its associations with obesity. This gene codes for a nuclear receptor that seems to have a major role in controlling expression of other genes involved in differentiation of precursor cells into adipocytes (fat cells), fat storage, and insulin sensitivity [32]. One *PPAR γ2* gene variant, a single nucleotide polymorphism that results in the substitution

of an alanine for a proline amino acid in the receptor molecule, seems to be *protective* against the development of diabetes, whereas the more common proline variant (present in 85% of whites and 95% of Japanese) seems to *increase* the risk of diabetes by approximately 25% [33,34]. The specific mechanism of action of this gene and gene variant is the subject of intensive investigation. Studies have identified several epistatic relationships (gene × gene interactions) between *PPAR γ2* and other genes that seem to modulate risk for type 2 diabetes [35–37]. Thiazoledinediones, a relatively new class of drugs used to treat type 2 diabetes, are agonists of the PPAR and seem to promote the increased storage of fat in adipocytes and reduced plasma free fatty acids. This activity decreases the impact of these toxic fatty acids on the development of insulin resistance, as described in further detail elsewhere in this article [38].

For the *PPAR γ2* gene, the fact that the "risk" genotype is the more common variant found in the population is of interest [39]. From an evolutionary standpoint, it would make little sense that a gene conferring risk for a deleterious condition such as diabetes would remain so prominently in the gene pool unless it had some survival advantage. Neel [40] surmised this when he proposed his "thrifty genotype hypothesis" in the early 1960s to explain the increasing rates of type 2 diabetes associated with societal progress and affluence. In earlier times when food was scarce and energy requirements were high, genotypes that promoted fat storage and lower metabolic rates were advantageous. In current times, when food is abundant and energy requirements are low, these genotypes are no longer advantageous and predispose to illness in the face of overnutrition and sedentary lifestyles. Although this hypothesis may not completely explain the prevalence of diabetes risk genes, it remains in consideration today [41–44].

Genetics of gestational diabetes mellitus

There are fewer studies of genetic factors associated specifically with GDM. Having a first-degree relative with type 2 diabetes is a risk factor for GDM, and GDM itself is a risk factor for the later development of type 2 diabetes. This situation suggests a high likelihood that genes predisposing to type 2 diabetes also are involved in GDM. A maternally transmitted factor has been proposed in the etiology of GDM because women who have a mother or grandmother with type 2 diabetes have a particularly high risk of developing the condition during pregnancy [45].

Genetics of diabetic complications

In addition to work on genes associated with the development of diabetes, studies have shown that particular complications associated with diabetes also tend to cluster in families [46]. Gene variants associated with diabetic complications such as nephropathy and retinopathy have been identified, as have variants associated with severity of complications [47–50].

Krolewski et al [51] suggested that genes predisposing to complications (eg, nephropathy) in type 1 diabetes are likely the same as the genes for type 2 diabetes, the shared environmental trigger being hyperglycemia. Further work in this area is important because it may identify valuable targets for future pharmacotherapy or gene therapy to reduce complications.

Environmental impacts on diabetes susceptibility

Environment and type 1 diabetes

Environmental exposure is believed to be a crucial factor in the progression to type 1 diabetes in genetically susceptible individuals [52]. An association of type 1 diabetes with early exposure to substances in cow's milk (possibly bovine insulin) was uncovered in the 1990s, although subsequent studies have produced mixed results [53–55]. More recent work has shown associations with enteroviruses, such as coxsackievirus infection, and with the timing of introduction of solid food proteins (gluten) into the infant diet [55–57]. Solid foods given either too early (before 3–4 months) or too late (after 7 months) seem to increase risk in genetically susceptible individuals [55,56]. It is suggested that these "foreign" agents trigger the pathogenic activation of T lymphocytes and the production of antibodies, which then are misdirected at various components of pancreatic beta cells, including the insulin molecule itself. Eventually these antibodies destroy the ability of the pancreas to produce and secrete insulin. The exact mechanisms by which environmental agents work in concert with genes to cause this disease are not sufficiently known to provide clear options for prevention.

Obesity and type 2 diabetes

The suspected connections between type 2 diabetes and obesity are valuable to explore at some length given their relevance to diabetes prevention efforts. Obesity is considered a primary risk factor for the development of type 2 diabetes. Sargeant et al [58] estimated that 38% of the excess risk associated with a family history of diabetes could be avoided if body mass index was not allowed to exceed 30 kg/m^2. How obesity exerts its effect is not fully understood, but it may be through metabolic effects described in further detail subsequently. Obesity-related metabolic abnormalities may compound or amplify the numerous baseline abnormalities found in genetically susceptible individuals with a family history of diabetes.

Although obesity seems to increase the risk of diabetes, this risk may be fairly limited in the absence of a genetic risk for diabetes. Estimates suggest that nearly 70% of type 2 diabetics are overweight or obese (body mass index >27 kg/m^2), but only 30% of individuals in the very obese category (body mass index >35 kg/m^2) actually have diabetes [58,59]. Although most children and adolescents who are being diagnosed now with type 2 diabetes

are overweight or obese, childhood diabetes is unlikely in the absence of a strong family history of diabetes and high-risk ethnicity [10]. Goldfine et al [60] suggested that obesity has minimal effects on risk of diabetes in individuals without a family history, but it significantly increases the risk of diabetes in individuals with a family history. In their population-based study, nonobese individuals with a family history of diabetes had an age-adjusted incidence rate of 8.8 per 1000 person-years for the development of diabetes versus an incidence rate of 1.6 per 1000 person-years in the nonobese population without family history. For obese individuals, the incidence rate for diabetes increased to 16.7 per 1000 person-years in the family history group, but only increased to 1.8 per 1000 person-years in the non–family history group.

Relatives of nonobese type 2 diabetics are at particularly high risk of developing diabetes. Work by a several groups supports the hypothesis that nonobese individuals with diabetes carry a "greater load" of diabetes susceptibility genes or possibly more potent genes [61,62]. In these individuals, excess adiposity does not seem to be a prerequisite for the development of the disease. Family members of these nonobese diabetics, whether or not they themselves are overweight, are at higher risk of developing the disease than family members of obese diabetics [62].

Numerous studies have suggested that individuals with a genetic predisposition to diabetes also are more likely to be obese or overweight [63,64]. This suggestion has led to the hypothesis that the metabolic processes underlying diabetes may contribute to the development of obesity in the first place. DePergola et al [65] showed that individuals with a family history of diabetes have reduced resting energy expenditure and decreased lipid oxidation measures compared with individuals without a family history. Both of these processes may result in excess weight gain in the presence of overnutrition or inactivity.

Even in the absence of a diagnosis of diabetes, a significant proportion of obese individuals are found to be insulin resistant. The insulin resistance syndrome or metabolic syndrome is an increasingly recognized obesity-associated entity that includes abnormal glucose tolerance (or insulin resistance in the presence of normoglycemia), hypertension, and dyslipidemia [66]. Risk for cardiovascular complications is particularly high in individuals with this syndrome. Although insulin resistance syndrome and type 2 diabetes are not equivalent, 70% of individuals with type 2 diabetes have the features of this syndrome [67].

Current theories suggest that the accumulation of excess fat in nonadipose tissue is a key factor leading to the development of the insulin resistance of obesity [67,68]. When adipose tissues reach capacity or if there are abnormalities in the normal processing and use of fats, excess fat is diverted and stored in nonadipose tissues (eg, muscle, liver). In these tissues, the fats enter pathways that generate damaging lipotoxins and inflammatory mediators, including free fatty acids. These mediators eventually cause

damage to the host tissues. Lipotoxic effects on skeletal muscle and other peripheral tissues may play a primary role in the development of insulin resistance. Lipotoxins also may play a role in damaging pancreatic beta cells, eventually leading to decreased insulin production and secretion and contributing to the development of diabetes.

New evidence suggests that lipotoxins and inflammatory mediators also may interact with genes to affect insulin sensitivity. Researchers have implicated the *JNK* (c-Jun amino-terminal kinases) gene in mice as potentially having a key role in the insulin resistance associated with obesity [69]. This gene seems to be activated by inflammatory mediators and free fatty acids. Increased activity of this gene is linked with the development of reduced insulin sensitivity (ie, insulin resistance), hyperinsulinemia, and hyperglycemia in mice in the presence of a high-fat diet and obesity. Obese mice that lacked the gene had greater insulin sensitivity, lower insulin levels, and lower blood glucose than obese mice with the gene. Further elucidation of a possible role for the *JNK* gene in human obesity-associated insulin resistance and type 2 diabetes will be important.

PPAR γ2 has been implicated in obesity and type 2 diabetes. The proline variant, which is associated with increased risk of diabetes, also is associated with increased body mass index and waist circumference. The effect of *PPAR γ2* on obesity seems particularly potent in the presence of other gene variants, including one common variant (Trp64-Arg) in the β_3-adrenergic receptor gene [70].

Fetal environment and type 2 diabetes and gestational diabetes

For type 2 diabetes, there has been considerable interest in more recent findings regarding fetal and perinatal factors associated with the development of type 2 diabetes. Numerous studies have confirmed an association of low birth weight with type 2 diabetes and GDM [71–73]. Excess weight gain in childhood after a period of relatively limited growth in early life is associated particularly with the eventual development of type 2 diabetes. To explain these associations, Hales and Barker [74] proposed the "thrifty phenotype" hypothesis, in contrast to Neel's "thrifty genotype" hypothesis. The phenotype hypothesis suggests that poor nutrition during fetal life leads to fetal adaptations that are beneficial in the face of inadequate nutrition but deleterious in the face of later overnutrition. Permanent changes in insulin sensitivity and glucose and lipid metabolism may occur and may involve an overall decrease in pancreatic cell mass. Frayling and Hattersley [75] suggested that a genetic variant shared by parent and fetus, a "thrifty genotype," may be responsible for an effect on fetal growth and the risk of diabetes. They provided evidence that genetic factors that predispose to insulin resistance and adult diabetes also lead to impaired insulin-mediated fetal growth.

Fetal exposure to a hyperglycemic environment in utero also is associated with the eventual development of type 2 diabetes [20,76]. This is the case

even if the mother has type 1 diabetes rather than type 2 diabetes. This effect may be through overstimulation of the fetal pancreas during exposure to elevated maternal glucose levels with subsequent pancreatic atrophy after the increased stimulus is removed at birth [20]. Whether maternal hyperglycemia alters fetal gene activity is not known, but this is one possible mechanism that could lead to changes associated with the later development of diabetes.

Applying genetics to diabetes prevention

Although there is still much to learn about the genetics of diabetes and the mechanisms by which environmental and behavioral factors interact with genes to affect diabetic risk, there are many ways that current information can be applied to clinical practice today to assist with prevention of diabetes and its complications. As knowledge in this area grows, additional applications will be possible. This section explores current and potential future applications of genetics to diabetes prevention.

Genetics and type 1 diabetes prevention

Overview

Intense research efforts are under way to find an effective primary prevention strategy for type 1 diabetes. Despite the lack of definitive prevention, it is currently possible to identify individuals who are at increased risk of developing disease [77]. At this point, the value of identifying high-risk individuals largely may be to society rather than to the individuals themselves. These high-risk individuals constitute the bulk of disease prevention study populations and are the greatest source of hope for finding an effective prevention strategy.

Predicting who is at risk for type 1 diabetes

Family history assessment is a first-line strategy for identifying individuals with genetic risk for type 1 diabetes. As discussed previously, children with a parent or sibling with type 1 diabetes are at particularly high risk of developing the disease. Primary care clinicians who care for children should collect and remain alert to family history of type 1 diabetes. When caring for patients with type 1 diabetes, it also is important to identify siblings and other family members who may be at risk. Couples who have a child with type 1 diabetes and who are considering additional pregnancies may benefit from genetic counseling to put the familial risk into perspective.

Although genetic testing for type 1 diabetes is not currently available as a tool for routine medical care, this technology is available to families in clinical research studies, such as the recently completed Diabetes Prevention Trials—Type 1 and the newly forming Diabetes TrialNet [78,79]. Current genetic susceptibility tests focus primarily on disease-associated HLA gene variants. When identified, individuals with high-risk genotypes can be followed for the development of autoantibodies that closely predict development of diabetes. Valuable resources for at-risk families are available through the American Diabetes Association, the National Institute of Diabetes and Digestive and Kidney Diseases, and the Juvenile Diabetes Research Foundation [80–82].

Population-based screening for high-risk genotypes has been proposed as another mechanism for identifying high-risk individuals. Many ongoing large-scale studies have investigated the feasibility and potential usefulness of newborn screening for high-risk HLA genotypes in identifying children who will go on to develop type 1 diabetes. These studies have included the Prospective Assessment in Newborns of Diabetes Autoimmunity (PANDA) study in Florida, the Diabetes Autoimmunity Study in the Young (DAISY) in Colorado, and several European studies [83–87]. These studies have suggested that screening is feasible using newborn blood spot screening and is well accepted by parents. Florida has initiated a statewide voluntary population-based screening protocol to identify high-risk children using newborn blood spot screening samples [88]. Although these approaches may be effective at identifying some individuals with risk genotypes, not all at-risk individuals will be identified, and many of persons identified will not go on to develop disease. The best positive predictive value was 20% in a Swedish population with a low sensitivity of 34% [89]. In addition to concerns about low predictive value, lack of effective prevention strategies raises ethical concerns, including the potentially adverse psychological effects of being labeled "at risk" [90]. Despite these concerns, population-screening studies conducted under well-controlled circumstances and with appropriate precautions can further understanding of the natural history of type 1 diabetes and point to possible prevention strategies.

Intervening before development of type 1 diabetes

Many of the type 1 diabetes prevention trials currently under way involve interventions in individuals who already have gone on to develop early signs of disease (ie, autoimmune markers reflecting pancreatic beta cell damage). In a commentary on these prevention efforts, Schatz et al [91] suggested that perhaps a new approach, initiating preventive strategies before beta cell destruction, might offer the best chance of preventing the disease.

Evidence linking type 1 diabetes with infant feeding practices (eg, solid foods and milk products) raises the possibility that avoiding exposure to these triggers may be helpful in preventing disease. There is little evidence to support strong recommendations for changing infant feeding practices [9]. Nevertheless, it seems prudent to encourage breast-feeding for at-risk infants and adherence to current schedules for introducing solid foods (ie, at 4–6 months).

Intervening early in type 1 diabetes to prevent long-term complications

In contrast to adults who may develop microvascular complications secondary to many years of chronic hyperglycemia with undiagnosed type 2

diabetes, children who develop type 1 diabetes typically are diagnosed before they have been exposed to a long duration of hyperglycemia. Nevertheless, being able to identify the earliest signs of disease in at-risk individuals may prevent life-threatening episodes of diabetic ketoacidosis and other signs and symptoms typically present in the early stages of undiagnosed type 1 diabetes.

Trials are under way to test many strategies in preventing type 1 diabetes progression in genetically susceptible children who already have begun to show signs of autoimmune beta cell destruction. The Diabetes Prevention Trials—Type 1 showed that neither daily injectable insulin nor oral insulin was effective in preventing progression to type 1 diabetes [92,93]. Monoclonal antibodies to suppress immunity and prevent or slow the destruction of pancreatic beta cell function currently are being investigated with some promising preliminary evidence [94]. Gene therapy also is being considered in animal and in vitro models to increase beta cell resistance to autoimmune cell destruction [95]. Much more research is needed before these measures are clinically applicable.

Genetics and type 2 diabetes prevention

Overview

In contrast to type 1 diabetes, there is good evidence from large trials in the United States and Finland that many cases of type 2 diabetes can be prevented or delayed, either with lifestyle intervention (diet, exercise, and weight loss) or with medication (metformin) [16,96]. The Diabetes Prevention Program showed that in prediabetic individuals (abnormal glucose tolerance with blood glucose levels below the diabetic range), a moderate regimen of diet, physical activity, and weight loss led to a 58% reduction in risk for progression to diabetes, and compliant use of metformin led to a 31% reduction in risk at 3-year follow-up. The incidence of progression in 3 years from prediabetes to diabetes was 11% in the nonintervention group, 4.8% in the lifestyle group, and 7.8% in the metformin group [16]. Of the participants, 70% in each control and intervention group had a known family history of diabetes, and 45% in each group was from an ethnic minority group. The groups were not stratified for family history, so it is unclear if individuals with a family history were more, less, or equally likely to benefit from the interventions. Despite this missing information, these data suggest that at least some genetically susceptible individuals can reduce diabetes risk with lifestyle change or medication. The Finnish studies showed equally good results with changes in diet and exercise [96].

Predicting who is at risk for type 2 diabetes

As for type 1 diabetes, family history assessment is the primary strategy available to determine who is at increased genetic risk for developing type 2 diabetes and its complications. Family history also may be valuable because

it typically reflects shared environmental risks. There are currently no genetic tests of type 2 diabetes gene mutations available for clinical use. Given the difficulties in nailing down specific gene-disease associations with certainty, it is unlikely that clinically valid and useful genetic tests to predict type 2 diabetes risk will be available soon.

Although there have been a few limited studies looking at general family history assessment practices in primary care settings, there is a lack of information regarding how diabetes family history information currently is collected and used in primary care [97]. There also is limited information on the most effective ways to collect and use this information for targeted disease prevention efforts. Developing and implementing family history tools that help guide diabetes prevention practices is currently an area of interest for public health and preventive medicine researchers [98,99].

Despite the lack of definitive information about the best way to collect and use family history data, primary care clinicians can incorporate available information about the genetics of type 2 diabetes into current practices to identify individuals who are at increased risk for disease. Many possible strategies may be effective in primary care, including the following:

- Construction of multigenerational family pedigrees that incorporate all the various diseases and conditions that are present in particular families (the gold standard genetic risk assessment tool used by genetic counselors and genetic medicine specialists)
- General family history screening for a variety of health conditions and disorders, including diabetes (a common approach in current primary care practice)
- Targeted questioning specifically focused on family history of diabetes
- Use of diabetes risk assessment tools that include family history as one of several risk variables
- Identification of at-risk family members of individuals with confirmed diagnoses of diabetes

Construction of pedigrees, although they yield a wealth of information, may be too time-consuming and impractical to implement in primary care. Acheson et al [100] reported that some primary care physicians do complete pedigrees on their patients, although this practice seems fairly limited (only 11% of charts in a primary care practice had a completed pedigree), and it is unclear how complete or up-to-date these pedigrees are. In the same study, it also was noted that although family history assessment activities were included in many primary care visits, time spent on these activities was minimal (an average of 2–3 minutes per visit in which some aspect of family history was discussed). Scheuner et al [101] proposed a modified pedigree approach to assess individuals for risk of chronic conditions of adulthood, including cardiovascular disease and type 2 diabetes. Couples attending a prenatal clinic provided family history information about specific chronic diseases, which was incorporated into a pedigree by a genetic counselor.

The number of affected relatives, degree of relationship, and age of onset determined risk status for the various conditions. Although this method could be used to categorize individuals as high, moderate, or low risk for diabetes, further study is needed to determine how the approach would work in routine primary care and whether this level of detail is necessary for initiating prevention strategies. Because of limited time available in clinical visits, it may be helpful to have patients work on constructing their own pedigrees or family trees outside of the office setting [100]. An approach that builds on public interest in genealogy and promotes construction of "family health trees" using tools such as those developed in the successful Health Family Tree study in Utah may be valuable [102].

Although use of pedigrees seems limited, general family history screening is a standard component of primary care. There are few data on exactly how this screening is conducted or how the information generated is used. This approach includes family history questionnaires that list a variety of genetically influenced disorders. A screening approach may be useful in identifying risk for diabetes if the information contained on the questionnaires is reviewed and prompts further inquiry or action steps. Additional questions that assess the pattern and extent of disease in the family are important to give a complete picture of genetic risk. These questions would include which relatives were or are affected (first-degree relatives suggest higher risk), age of onset (earlier onset suggests increased genetic risk), associated conditions (lack of obesity suggests increased genetic risk; presence of obesity and hypertension suggests metabolic syndrome, which also seems to be genetically mediated), and specific disease complications (specific complications seem to be under genetic influence and cluster in families).

Intentional targeted questioning about family history of diabetes may have some merit as an approach if applied systematically in a clinical population. Pinsky et al [103] described this as a "triage" strategy for collecting family history information. This approach would focus clinician attention specifically on diabetes, would reduce time spent on individuals who are unlikely to be at increased genetic risk for disease, and could prompt further questioning and characterization of risk in individuals with a family history. Such an approach could be used in adult and pediatric populations for type 1 and type 2 diabetes risk assessment.

Along a similar line of reasoning, targeted diabetes risk assessment strategies also may be useful in identifying individuals with increased susceptibility to type 2 diabetes. Many diabetes risk scoring techniques that include family history have been described. These risk scores seem to have good sensitivity and specificity for identifying individuals who are likely to go on to develop diabetes, but they are complicated to calculate [104–107]. Herman et al [108] described a simple self-administered screening tool that could be adopted easily in clinical practice. This tool includes questions related to parental history of diabetes and sibling history. Personal history of GDM or delivery of a macrosomic infant also is included. Age, body mass index, and level of physical activity are other variables considered. Although the positive predictive value of this tool for identifying undetected diabetes is fairly low (10%), because it is user-friendly, it may be particularly helpful in opening discussion with patients. The tool has been modified and adopted by the American Diabetes Association and is being incorporated into the US Department of Health and Human Services' Diabetes Detection Initiative launched in November 2003 [109,110].

Because patients with diabetes compose a significant proportion of primary care caseloads, it would make sense to start with them to identify family members who are at elevated risk of diabetes. Gnanalingham and Manns [111] suggested that individuals with type 2 diabetes may not be aware of the risks to their family members, but are receptive to this information and willing and motivated to share familial risk and risk reduction messages with loved ones. Although no one strategy for using family history currently can be recommended over another, increased recognition by primary care clinicians of the importance of identifying individuals with genetic risk for type 2 diabetes and adoption of any of the strategies would represent an important advance.

Intervening before development of type 2 diabetes

As discussed previously, it is possible to identify many individuals who are genetically and behaviorally at risk for type 2 diabetes and to intervene before the development of the disease. These data make a strong case for aggressive pursuit of lifestyle modification in high-risk individuals and families. Increased physical activity, even in the absence of weight loss, can be beneficial in individuals with a family history, as evidenced by the work of Sargeant et al [58] in the European Prospective Investigation into Cancer (EPIC)–Norfolk study. Simple changes, such as reducing television viewing, can have significant benefits, decreasing the risk of diabetes [112].

Continued research into the factors involved in prompting individuals who are at risk for diabetes to make lifestyle changes is needed [113]. Behavioral science researchers have begun to look at whether targeted genetic risk information can have a positive impact on behavior change. It is appealing to think that family history and genetic risk information could be used as a motivator for action. Behavior change is a complex process. Individuals who are most likely to change their behavior to reduce their risk of developing a disease such as diabetes are those who (1) perceive the condition to be harmful, (2) perceive that they are personally at risk to develop the condition, and (3) perceive that they have some control over their risk [114]. Risk perception studies have suggested that although some individuals with a family history of diabetes underestimate their risk of disease, many individuals with a family history do perceive the disease to be serious and themselves to be at increased risk; they may be more likely to participate in health behaviors that reduce risk, such as weight control efforts [115–117]. Some individuals believe that although family history

increases their risk of disease, they have little control over that risk. These individuals may be less motivated to change behavior in the face of genetic risk information [118]. Even if individuals are motivated by genetic risk information, studies of lifestyle interventions in overweight individuals with a family history of diabetes suggest that maintaining behavior change is challenging. Outcomes may not be significantly better from knowing one's genetic risk [119,120].

Further work in this area should provide valuable insights for primary care clinicians working with and communicating with at-risk patients. For now, exploring individual perceptions about diabetes, about the family history, and about personal risk reduction all may help to guide meaningful physician-patient communication. For individuals who tend to view genetics with a fatalistic perspective, de-emphasizing the role of genes in diabetes and stressing the benefits of lifestyle change may be most effective [118]. For others, genetic and familial risk information may be helpful as a trigger to adopt healthier behaviors. Providing individuals who have a diagnosis of type 2 diabetes with information about the familial aspects of the disease and encouraging them to educate their own family members about risk, risk reduction measures (diet, exercise, and weight control), and screening practices may be another effective strategy [111]. Targeting parents, particularly parents with a family history of diabetes and parents in high-risk ethnic groups, with information about the risk of type 2 diabetes to their children and the benefits of establishing healthy behaviors at an early age, including healthy eating habits and reduced sedentary behaviors (eg, television and computers), also may be valuable.

Even if everyone were to adopt a healthy lifestyle and maintain a healthy weight, some individuals likely still would develop type 2 diabetes. Type 2 diabetics who are not overweight and their at-risk family members are a group that has received relatively little preventive attention. Weight control and exercise, although valuable for general health maintenance, may not be as effective in preventing diabetes in these individuals with a "greater load" of genetic susceptibility genes. Different strategies (eg, pharmaceutical approaches) may be necessary to prevent development of the disease. In the absence of primary prevention, secondary prevention of diabetic complications may be possible through close monitoring and early identification of the disease with subsequent aggressive glycemic control. The fact that these individuals may not be visibly at risk for diabetes (ie, not overweight) highlights the need to screen and assess all patients for a family history of diabetes, including the pattern of disease present (ie, whether or not the disease is associated with obesity).

Intervening early in type 2 diabetes to prevent or reduce complications

With the growing prevalence of type 2 diabetes, the fact that the disease can be identified in an early asymptomatic prediabetes phase, and the fact that effective interventions are available, screening for type 2 diabetes has become a topic of considerable discussion and debate. Currently, universal screening for type 2 diabetes in the absence of cardiovascular risk factors is not recommended because no randomized, controlled trials have shown the effectiveness of this approach in reducing diabetes or its complications [121]. Despite this stance, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus has issued screening guidelines to identify most individuals who have prediabetes or undetected diabetes for early treatment [5]. Family history of diabetes in a first-degree relative is an important component of these guidelines and should prompt consideration of glucose testing before age 45 years, especially in the presence of other risk factors, such as obesity or hypertension.

Individualizing treatment of type 2 diabetes to optimize outcomes

Perhaps the greatest impact that genetic advances will have on the secondary and tertiary prevention of type 2 diabetes (and perhaps even primary prevention) will be in the area of clinical pharmacogenetics [122]. Tailoring drug therapy based on an individual's genotype and his or her own unique pattern of disease holds the promise of optimizing response to medication treatment, decreasing the risk of adverse drug reactions and improving outcomes. Genotypes that increase risk of particular diabetic complications also could be targeted to reduce or prevent the development of these complications. Pearson et al [123] reported a study of patients with a *HNF-1α* mutation (one of the MODY gene mutations resulting in an early-onset form of type 2–like diabetes). They found that hyperglycemia in individuals with *HNF-1α* was highly responsive to the sulfonylurea gliclazide and poorly responsive to metformin. As new genes that play a role in diabetes are identified, drug treatments targeting these pathways can be developed.

Genetics and gestational diabetes prevention

Predicting who is at risk for gestational diabetes

As with type 2 diabetes, there are no genetic tests currently available to determine who is at risk for GDM. Family history of type 2 diabetes and a history of previous GDM are indications for screening early in pregnancy.

Intervening before pregnancy

There is good evidence that glycemic control in women who have diabetes before pregnancy improves pregnancy outcomes, including reduced incidence of congenital anomalies [124]. Because GDM arises as a result of factors specifically associated with pregnancy, little work has been done to determine whether exercise and weight control measures before pregnancy in women who have increased familial risk of the condition are an effective approach to preventing GDM. More work is needed in this area.

Intervening early in gestational diabetes to prevent complications

There has been increased focus on identifying women with GDM earlier in pregnancy and intervening to prevent complications [125]. Current guidelines recommend that certain at-risk individuals be screened as early in pregnancy as possible to identify signs of glucose intolerance, rather than waiting until the usual 24 to 28 weeks of gestation [126,127]. High-risk individuals include women with a strong family history of diabetes (ie, in a first-degree relative or multiple relatives). All pregnant women should be assessed at the first prenatal visit for diabetic risk factors, including family history and obesity. Prompt oral glucose tolerance testing is recommended in women found to be at higher risk. Repeat testing at 24 weeks is recommended for these women if initial tests are normal.

Maintaining glycemic control in pregnancy is associated with better health outcomes for infants [128]. Recognizing women earlier in pregnancy and optimizing glycemic control may have added benefits beyond improving pregnancy outcomes. As previously described, infants born to diabetic mothers are more likely to have diabetes themselves as adults. This effect seems to be due not solely to shared genetic risk, but also due to exposure of the fetus to a hyperglycemic environment [45]. Multigenerational studies are needed to measure the benefits of identifying and treating women early in pregnancy or before pregnancy to avoid this fetal exposure.

Intervening to prevent type 2 diabetes in individuals with gestational diabetes

Individuals with GDM are at significantly increased risk of developing type 2 diabetes later in life. Weight gain during the years after pregnancy is a primary factor in this progression to type 2 diabetes [129]. Ensuring that women who have had GDM are educated about their future risks for developing type 2 diabetes and assisted with risk reduction strategies is an important role of the primary care clinician.

Summary

There is much still left to learn about genetics and diabetes and how this information can be applied to clinical disease prevention efforts. Primary care clinicians would be well advised to stay tuned for emerging evidence and approaches that have a potential to reduce the enormous burden that diabetes places on society. In considering type 2 diabetes, a quote by Brenner comes to mind. In an editorial for a 2003 *Science* magazine issue devoted to the topic of genomic medicine, Brenner wrote: "Many people base their lives on the proposition that they can do what they like to their bodies because medical science will come save them with a pill. Perhaps the prime value of our work to society will be the creation of a new public health paradigm in which we are all taught how to look after our somatic selves; those who have a genetic background that makes them especially liable to one of the diseases of civilization will have to learn how to take extra care" [130]. In this paradigm, primary care clinicians have crucial roles in identifying genetically susceptible individuals and helping them learn how to take that extra care.

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ELSEVIER SAUNDERS

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PRIMARY CARE: CLINICS IN OFFICE PRACTICE

Clinical consult: iron overload—hereditary hemochromatosis

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Case

A 58-year-old man presents to his primary care physician with weight loss and increased skin pigmentation. His past history is significant for diabetes mellitus, joint pain, and impotence. The patient reports consuming approximately three alcoholic drinks per week and denies a history of anemia or iron supplementation. He has an older brother with liver cirrhosis, an older sister with arthritis, and two younger brothers who are both reportedly in good health. The patient has three healthy children.

Iron overload results from genetic and nongenetic causes. One of the most common genetic causes of iron overload is hereditary hemochromatosis (HHC), a condition characterized by overabsorption of dietary iron from the gastrointestinal tract. This condition can lead to excessive iron accumulation with resulting dysfunction in multiple organs, including the liver, skin, heart, joints, pancreas, and testes. The clinical consequences of HHC if undetected and untreated can be severe and include liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, cardiac arrhythmias and failure, arthritis, and hypogonadism. HHC is one of the most common heritable conditions in white populations of Northern European origin. It is

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